AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

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IN THIS ISSUE

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A NEW HUMAN T-LYMPHOTROPIC RETROVIRUS: CHARACTERIZATION AND POSSIBLE ROLE IN LYMPHADENOPATHY SYNDROME AND AIDS

The T-lymphotropic retrovirus (LAV1) isolated from a patient with lymphadenopathy syndrome (LAS) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871) has been further characterized. Cultured T lymphocytes from either umbilical cord or peripheral blood of healthy, virus-negative, adult donors were suitable for virus propagation (Ibid; Vilmer E, Barré-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). Virus production usually started 9-15 days after infection and lasted for 10-15 days. In no case was the emergence of a continuous permanent line observed.

Electron microscopy of ultrathin sections of virus-producing cells showed two types of virus particles. These were presumed to correspond to the immature and mature forms of the virus. The immature particles were seen to bud at the cell surface, with a dense crescent in close contact with the plasma membrane. Ribosome-like structures could sometimes be observed in these particles. Mature particles had small, dense, eccentric cores of mean diameter = 41 nm. Most of the virions were round (mean diameter = 139 nm) or ovoid. In some pictures, a tailed morphology could also be observed. This form was seen in particles in cytoplasmic vesicles released into the medium; it was first observed in particles in the original culture from which the virus was isolated.

The morphology of mature LAV particles is clearly distinct from the morphology of human T-cell leukemia virus (HTLV) particles. Both mature and immature forms of LAV were morphologically similar to particles of equine infectious anemia virus (EIAV) (Tables 1 and 2).

TABLE 1
COMPARISON OF LAV1 AND HTLV1

Similarities	Differences
1. Human retroviruses	1. Major core proteins, LAV p25, HTLV p24, not antigenically related
2. Mg^{++}-dependent reverse transcriptase	2. Morphology (EM): Eccentric core in LAV half the size of HTLV core
	3. Co-cultivation not required for infection of lymphocytes with LAV1
	4. No immortalized T-cell line obtained after LAV infection to date

The main protein isolated from LAV had a molecular weight of 25,000 daltons (p25). It was the only protein recognized by serum from the patient from whom it was isolated. Immunoelectron microscopy experiments showed that the protein is located in the viral core: viral cores could be agglutinated by the patient's serum (S. Rousset, personal communication). Major proteins of other retroviruses have also been shown to be core-associated.

No homology was found between p25 of LAV1 and p24 of HTLV (types 1 and 2) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871). Antisera against p24 and p25 did not

TABLE 2
COMPARISON OF LAV1 AND EIAV

Similarities	Differences
1. Retroviruses	1. Target cells are not the same in vitro and in vivo
2. Mg++-dependent reverse transcriptase	2. LAV1 does not grow in fibroblastic human lines nor in equine dermis cell line
3. Morphology (EM): eccentric asymmetric core	
4. p25 proteins antigenically related	
5. Active production (with cytopathic effect) in a small proportion of infected cells	
6. Same pattern of major polypeptides: core protein = p25 envelope protein = gp40? p15?	

cross precipitate the two proteins. No cross-reactivity was found between LAV1 and bovine leukemia virus, feline leukemia virus, or simian sarcoma-associated virus. A weak cross-reactivity with EIAV was detected through immunoprecipitation of polyacrylamide gel electrophoresis bands using an antiserum against p25. However, immunodiffusion tests using sera from patients positive against LAV1 did not show a precipitin line to EIAV antigens (B. Toma, personal communcication). Preliminary experiments showed no homology between DNA from LAV1-infected cells and an HTLV DNA probe, even under low stringency of hybridization conditions (F. Wong-Staal, personal communication).

The majority of cultured T cells isolated from the patient's lymph node reacted with homologous serum in immunofluorescence studies of fixed cells. (The main antigen recognized in this test is presumed to be p25 viral protein.) Therefore, even though production of mature virions as detected by reverse transcriptase (RT) activity was rather low, most of the cells in culture were infected with the virus and expressed viral proteins. When the virus was propagated in lymphocytes from normal donors, only between 2 and 10% of cells contained virus, as indicated by immunofluorescence studies of fixed cells, at the peak time of virus production. Increasing the amount of virus used to infect the cells did not result in an increase of virus production. From normals, therefore, only a minority of T cells were in a state conducive to virus production.

When lymphocytes were fractionated into subsets and infected with LAV1 (D. Klatzmann et al, in preparation), the virus showed an obvious tropism for the OKT4+ subset. Immunofluorescence staining indicated that approximately 10% of the OKT4+ cells expressed viral antigens. The OKT4+ phenotype remained unchanged during virus production. No gross changes, such as cell lysis or impairment of cell growth, could be seen in virus-producing cultures. However, since only a minor fraction of T-helper cells seems to produce virus, a specific cytopathic effect on this subset cannot be excluded.

OKT8+-enriched cell cultures infected under the same conditions did not produce any detectable RT activity, even 6 weeks after virus infection. Adherent cells (macrophages) and B cells after

mitogenic stimulation also did not produce virus. Preliminary experiments with bone marrow cells suggested that immature (OKT3-depleted) cells could be infected and produce virus.

The tropism for helper T cells may also exist in vivo. A healthy black Caribbean woman carried a virus similar or identical to LAV1 in blood lymphocytes. When these cells were fractionated into subsets, put in culture, and stimulated, only the OKT4+ subset produced virus as detected by RT activity.

Activated lymphocytes from a healthy donor which were spontaneously releasing a virus similar to LAV1 in culture were infected in vitro with LAV1. A few giant polycaryons appeared in these cultures after a lag of 6-7 days. Electron microscopic examination showed numerous particles of the LAV type budding at the cell surface. Examples of progressive cell fusions were also seen. The giant cells rapidly degenerated in the cultures. HTLV-producing cell lines (Popovic M, Sarngadharan MG, Read E, et al: Science, 1984, 224:497-500) also include giant cells which probably arise from virus-induced cell fusions.

It is possible that cell-fusion activity, after repeated infections with LAV1 or similar retroviruses, could lead to the degeneration of a fraction of the T-cell population. Viral proteins at the plasma membrane (and perhaps in other membranes) of host cells could greatly affect specialized functions of the cells. The degeneration of giant cells may represent the extreme situation of viral cytopathic effects.

Cells of lymph nodes from five other LAS patients were put in culture. No virus production could be detected (as measured by RT activity). However, antiserum from the original patient detected a p25 protein in cytoplasmic extracts of T cells in three cases. All of the six LAS patients had antibodies against LAV p25, indicating that all had been infected at some time with a similar or identical virus. From lymphocytes of one of the patients, a p24-p25 band showed weak but definite immunoprecipitation with goat antiserum raised against HTLV1. The patient's serum had antibodies against both HTLV and LAV1, suggesting a double infection.

LAV1 or LAV-like viruses were also isolated from lymphocytes taken from lymph nodes or blood of individuals with authentic cases of AIDS (see accompanying paper). The retroviruses (referred to as immune deficiency-associated viruses [IDAV1 and IDAV2]) of two of the AIDS cases have been propagated on normal lymphocytes and partially characterized. So far, they are similar if not identical to LAV1. The virus yield from lymphocytes from one blood donor was three to four times higher when cells were infected with IDAV1 or IDAV2 than when they were infected with LAV1.

The viruses have the main characteristics of retroviruses. LAV1 shows measurable Mg^{++}-dependent RT activity in culture supernatants, a density of 1.16 in sucrose gradient, and morphogenesis by budding at the plasma membrane. Preliminary data show a fast-sedimenting RNA component. It is tropic for OKT4+ T-helper lymphocytes and has a slight cytopathic effect in cells actively producing virus.

While LAV1 is clearly distinct from HTLV (1 and 2) isolates, it shows some analogy to EIAV. The similarities between these two retroviruses include identical morphologies and common antigenic determinants of the major core proteins. EIAV infection causes lifelong severe infection in horses, characterized by bursts of fever with anemia. Each burst seems to coincide with the appearance of a new antigenic variant of

the viral glycoprotein (Issel CJ, Coggins L: J Am Vet Med Assoc., 1979, 174: 727-733). In LAS patients, antibodies against viral envelope proteins were not found in sera. If this is an indication that similar antigenic variations occur in LAV1, such variations may be relevant to how pathogenicity is accomplished by the virus. Both EIAV and LAV1 appear to be relatively stable: the LAV-related viruses isolated from a hemophiliac patient and from his brother were probably transmitted in blood-derived preparations in which they survived several steps of purification (Vilmer E, Barré-Sinoussi F, Rouzioux C: Lancet, 1984, 1: 753-757).

The evidence for the role of LAV and LAV-related viruses in LAS and AIDS, although indirect and circumstantial, is as follows: (1) The virus is present and expressed in cultured lymphocytes from LAS and AIDS patients in the majority of the cases investigated. (2) The virus replicates exclusively in OKT4 lymphocytes. These are the very cells depleted in AIDS. Although adsorption of the virus can take place in unstimulated blood lymphocytes, virus production by these lymphocytes requires stimulation and the continuous presence of T-cell growth factor. (3) Serologic data indicate that most of the LAS patients have been infected with LAV-related viruses, and only a minority with HTLV1 (see accompanying paper). (4) Based on the finding of LAV in the hemophiliac siblings, the virus seems to be transmissible through blood and blood products.

Final proof that LAV or a LAV-like virus plays an etiologic role in AIDS (and perhaps other diseases) will require confirmation of the initial results, additional data, and production of the disease in an animal system. The available data do allow us to draw a general outline for the virus etiology of AIDS.

We postulate that T-lymphotropic retroviruses--including LAV and HTLV-related viruses--are the primary agents of the disease. The primary infection in most cases would not be apparent, because only a small population of T lymphocytes (from blood, lymph nodes, bone marrow) would be infected and would integrate the viral genome. For the secondary phase, many antigenic stimuli (including repeated viral and bacterial infections) might stimulate the T-cell system, including the already infected lymphocytes. Stimulated, infected cells would actively produce virus; the virus could then infect other stimulated lymphocytes and diffuse throughout the T-helper system. This phase of the disease could sometimes be limited to lymph nodes and induce a lymph node hyperplasia (LAS). In the final phase, the whole T-cell population, including stem cells, would be infected, and the patient would be in danger of developing severe and irreversible immune deficiencies.

The exact mechanisms by which the retroviruses induce AIDS in this scheme remain to be determined. The simplest explanation would involve a direct cytopathic effect, and some of our data can support this explanation. It is also conceivable that insertion of viral proteins into the plasma membrane may disturb helper cell functions. Finally, an autoimmune disease may occur: infected cells could generate a host defense mechanism (interferon, cytotoxic cells) which in turn would affect T-cell multiplication and functions.

Clearly, AIDS is a complex disease in which many genetic and environmental factors are involved. The availability of molecular probes for human lymphotropic retroviruses will help greatly in

defining the exact role of such viruses in the disease.

This article includes information from a paper (Human T-Cell Leukemia/ Lymphoma Virus. The Family of Human T-Lymphotropic Retroviruses. Their Role in Malignancies and Association with AIDS, 1984) which will be published by Cold Spring Harbor Laboratory and is reprinted here with permission from the publisher.

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DETECTION OF IgG ANTIBODIES TO LYMPHADENOPATHY-ASSOCIATED VIRUS IN PATIENTS WITH AIDS AND WITH LYMPHADENOPATHY SYNDROME

An enzyme-linked immunosorbent assay (ELISA) was developed to determine whether specific IgG antibodies capable of reacting with the first isolate of lymphadenopathy-associated virus (LAV)--a new human retrovirus isolated from lymph node-cultured T lymphocytes of a homosexual man with lymphadenopathy syndrome (LAS) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220: 868-871)--were present in sera from various other patients with LAS and in patients with AIDS. ELISA results have been compared with results obtained by a radioimmune precipitation assay (RIPA) detecting antibodies to the LAV p25 protein. In addition, anti-human T-cell leukemia virus (HTLV1) antibodies and anti-cytomegalovirus (CMV) IgG antibodies have been measured in order to evaluate the possibility of correlations among these three immunologic markers.

Serum samples were obtained from five groups: 51 patients with LAS (as defined in Morb Mort Weekly Rep., 1982, 19:249-251), 48 patients with AIDS, 44 healthy homosexual men who visited a venereal disease clinic in Paris, 100 unselected blood donors, and 30 healthy laboratory workers.

The LAV ELISA was set up in Nunc™ ELISA microtiter plates. Details of the technique are in press (Lancet). The LAV RIPA method has been described elsewhere in detail (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871). HTLV1 p24 antibodies were measured with a commercial ELISA (Bionetics) or by radioimmunoassay (RIA). The IgG antibodies to CMV were titrated by ELISA (Schmitz H, Doerr HW, Kampa D, et al: J Clin Microbiol., 1977, 5:629-634).

The results of the various antibody assays are shown in the table. Antibodies to LAV were detected in 74.5% of LAS patients. In 11 of 12 of these patients for whom blood samples had been collected more than once during the disease, sera remained either positive or negative for LAV antibodies throughout the study. The 12th patient first developed antibodies to LAV 2 years after the onset of LAS. In 18 cases, antibodies to LAV p25 were also determined by RIPA. In 13 of these, ELISA and RIPA results were perfectly correlated. In the other five cases, antibodies could be detected by RIPA but not by ELISA.

Viruses similar to LAV were isolated from cultured T lymphocytes derived from lymph nodes of two additional LAS patients. Sera from both contained LAV antibodies. One of these two went on to

POSITIVE SERUM SAMPLES

	LAV IgG ELISA	p24 HTLV ELISA*	CMV IgG ELISA
LAS	38/51 (74.5%)	5/51 (9%)†	46/50 (92%)
Homosexual men	29/40	4/40	37/40
Drug addicts	6/8	0/8	6/7
Haitians	3/3	1/3	3/3
AIDS	18/48 (37.5%)	6/48 (12.5%)‡	45/46 (98%)
OI	12/30	5/30	
KS	3/12	0/12	
OI + KS	2/5	1/5	
Brain lymphoma	1/1	0/1	
B hemophiliac	1/1	0/1	
Homosexual men	10/35	4/35	
Haitians	3/4	1/4	
Africans	4/8	1/8	
Controls			
Homosexual men	8/44 (18%)	0/44 (<1%)	41/44 (93%)
Blood donors	1/100 (1%)	0/100	45/100 (45%)
Lab workers	0/30	0/30	ND

Abbreviations: CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; HTLV, human T-cell leukemia virus; KS, Kaposi's sarcoma; OI, opportunistic infection; LAS, lymphadenopathy syndrome; LAV, lymphadenopathy-associated virus; ND, not determined.

* When all sera were tested by p24 HTLV radioimmunoassay, only one from a homosexual man with LAS remained positive (L. Schaffar, personal communication).

† 3/6 were also LAV positive.

‡ 4/5 were also LAV positive.

develop AIDS. He is a French homosexual man who had lived for 2 years in Haiti (1980-81), developed a persistent fever in January 1982, LAS in March 1983, and mucosal and cutaneous KS in June 1983. Antibodies to LAV were first detected in January 1982, suggesting that viral infection had preceded other signs of disease.

There was no correlation between seropositivity to LAV and to CMV, since 92% of all LAS patients were positive for CMV IgG. There was also no correlation between decreases in T4:T8 ratios--in most cases resulting from increases in the number of cells in the OKT8 subset--and positivity for LAV antibodies.

Fewer patients with frank AIDS (37.5%) were positive for LAV. When tested by ELISA, 12.4% had HTLV1 antibodies, but none of the sera were positive for p24 HTLV1 antibodies when tested by RIA. In two of the AIDS patients, serologic studies began before the onset of AIDS. Both had LAV antibodies in the first serum samples tested. In one, the antibody titer decreased at the onset of AIDS; in the other, the antibody titer did not change. In two other AIDS cases, sera were analyzed during the development of AIDS. In one, the LAV titer remained positive throughout the test period; in the other, the titer shifted from positive to negative. In the latter, HTLV1 antibodies were also negative in the last sample tested, while the CMV IgG titer remained positive.

Sera of 25 AIDS patients were also tested for LAV by RIPA. In 18, RIPA and ELISA results coincided. In five, antibodies were detected by RIPA and not by ELISA. In two, antibodies were detected by ELISA but not RIPA.

Eighteen percent of healthy homosexual controls were seropositive for LAV antibodies. All but one seropositive individual had more then 50 sexual partners per year. None had HTLV1 antibodies, while most had CMV IgG. Only one blood donor and no healthy laboratory workers had LAV antibodies. The CMV IgG prevalence in controls was appropriate to a 30- to 40-year-old Northern European population (Boue A, Cabaun N: Nouv Presse Med., 1978, 7:3135-3139).

Retroviruses similar to LAV were isolated from several patients with frank AIDS. The viruses have been named immune deficiency-associated viruses (IDAV). IDAV1 was isolated from an AIDS patient with Kaposi's sarcoma. Serum samples from this patient were negative for LAV antibodies by ELISA but positive for IDAV1 antibodies in an ELISA in which IDAV1 was used as antigen. IDAV2 was isolated from peripheral lymphocytes of a B hemophilia patient. A virus similar to IDAV2 was isolated from the patient's healthy brother who was also a hemophiliac (Vilmer E, Barré-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). IDAV3 was isolated from peripheral blood lymphocytes of a Zairian woman who emigrated to France.

LAV and the IDAV isolates appear to belong to a new group of viruses which have the usual characteristics of retroviruses (see preceding paper). Despite imperfections and some differences in results depending on the assay used, the picture emerging from these studies is that a high proportion of patients with LAS have IgG antibodies to LAV, indicating prior or current infection with this or a related virus.

In the group of frank AIDS patients, the number of patients who were seropositive was significantly different from control groups but lower than the % positive in LAS patients. Two hypotheses have been suggested to explain this lower association.

First, LAV may be more closely related to LAS than to AIDS. LAV may be but one of the opportunistic viral agents found in AIDS, and other viruses may have a role in the onset of the disease. HTLV is one candidate. In our studies, none of the AIDS sera had antibodies to the HTLV1 major core protein by RIA. In other reports (Essex M, McLane MF, Lee TH, et al: Science, 1983, 220:859-862), antibodies to antigens expressed on the cell surface of HTLV1-transformed lymphocytes were detected in the sera of 25-36% of AIDS patients, 25-30% of patients with LAS, and 1% of matched homosexual controls or blood donors. More recent studies implicate HTLV3 isolates (Gallo RC, Salahuddin SZ,

Popovic M, et al: Science, 1984, 224: 500-502).

Alternatively, the severe immune impairment at the late stage of the disease may affect B lymphocytes (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458) such that a humoral response against viral proteins may become undetectable. A large proportion of the sera which were tested were in fact collected at late stages of AIDS. One AIDS patient who was LAV positive at presentation did become negative at a later stage. Similarly, the hemophiliac had a decreased titer of LAV IgG antibodies at the time of onset of AIDS, even though the IDAV2 retrovirus could continuously be isolated from his peripheral T lymphocytes.

There are indications that LAV infection is present in AIDS patients living in the US and in Equatorial Africa. Prospective seroepidemiological studies are required to confirm the involvement of LAV in AIDS. Comparative studies are currently underway on groups considered to be at risk for AIDS and on control populations in various countries.

Note added: LAV antibodies assayed by ELISA and RIPA were present in 94% of AIDS patients in Zaire and in only 19% of controls. In the positive controls (5/26), four controls had reversed OKT4: OKT8 ratios due to decreased circulating T-helper lymphocytes. In addition, two sexual contacts of AIDS patients in Zaire were also found to be positive for LAV antibody (T. Quinn, personal communication).

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PREVALENCE AND INCIDENCE OF CYTOMEGALOVIRUS INFECTIONS AMONG HOMOSEXUAL MEN

There is evidence that cytomegalovirus (CMV) infections can be transmitted by sexual contact, especially among homosexual men. In one study of male homosexuals in San Francisco, a very high prevalence of antibodies to CMV was found (94%); and 14% of the men under 30 years of age had CMV viruria (Drew WL, Mintz L, Miner RC, et al: J Infect Dis., 1981, 143:188-192). In a Danish study, the antibody prevalence among homosexual men was related to the duration of homosexual activity (Melbye M, Biggar RJ, Ebbesen P, et al: Acta Pathol Microbiol Immunol Scand [B], 1983, 91:357-364).

During a recent hepatitis B vaccine efficacy study, we followed a large group of homosexual men over a period of nearly 2 years (Coutinho RA, Lelie PN, Albrecht-van Lent P, et al: Br Med J., 1983, 286:1305-1308). This gave us the opportunity to study the prevalence and incidence of CMV infections among this group of men and the relationships of CMV infections to a number of risk factors.

A total of 710 homosexual men participated in this study. The mean age was 30.1 ± 7.0 years. The participants lived in and around Amsterdam. Blood samples were collected from the participants at monthly intervals for 5 months and every 3 months thereafter. The first and the last blood samples were tested for the presence of antibodies to CMV (anti-CMV). If either a seroconversion or a significant rise in titer was found, all samples taken in-between were tested. A primary CMV infection was defined as a seroconversion for anti-CMV for which anti-CMV IgM antibodies could be detected in at least two sequential blood samples. A recurrent CMV infection was

defined as a >4-fold rise in titer in a person already positive for anti-CMV; confirmation of the rise was required in at least one following blood sample.

Of the 710 men, 501 (70.6%) were found to have complement fixing antibodies to CMV at entry into the study; 209 (29.4%) were seronegative. During the follow-up, 69 CMV infections were detected. Fifty of these were primary infections among the seronegative participants; 19 were recurrent infections among the seropositive men. At the end of the study (23 months), the attack rate for primary infections was 27.3% and for recurrent CMV infections was 6.2%.

Using stepwise logistic regression analyses (Coutinho RA, Albrecht-van Lent P, Lelie PN, et al: Br Med J., 1983, 287:1743-1745), four characteristics of the participants were found to be correlated with seropositivity for CMV. The duration of homosexual activity had the highest correlation ($p < 0.002$). The probability of seropositivity increased 1-2% for each year of homosexual activity. This effect was independent of age. The next important risk factor was the number of different sexual partners in the preceding 6 months ($p < 0.03$), with the risk increasing with increasing numbers of partners. A history of syphilis and a history of anal sexual contact were also significantly correlated with seropositivity.

For seronegative men, the primary CMV attack rate was correlated with a history of syphilis (relative risk = 2.21) and anal sexual contact (relative risk = 2.49) as analyzed by life-table methods (Ibid).

The relatively low (70.6%) anti-CMV prevalence among the homosexual men in this study as compared with the prevalence (94%) in the San Francisco study is probably a reflection of the selection method for participants, all of whom were negative for hepatitis B markers. Among the 209 seronegative men, a very high primary CMV attack rate was found. Among the 501 seropositive men, the recurrent CMV infection rate was much lower. It is, however, difficult to draw a conclusion about the recurrent infections, as only serological data and not viral culture data were collected.

We conclude from this study that CMV infections are very prevalent among homosexual men and that anal sexual contact plays an important role in the transmission of the virus.

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REINFECTION WITH CYTOMEGALOVIRUS IN AIDS PATIENTS

Hirsch and his colleagues have shown that primary cytomegalovirus (CMV) infections induce transient immunosuppression (Rinaldo CR Jr, Carney WP, Richter BS, et al: J Infect Dis., 1980, 141:488-495). We have suggested that CMV may contribute to the etiology of AIDS: repeated episodes of primary CMV infections with different strains of CMV could perpetuate a state of immunosuppression (Drew WL, Miner RC, Ziegler JL, et al: Lancet, 1982, 2:125-127).

To determine whether multiple and different CMV infections actually occur, we have studied autopsy tissues from

four AIDS patients. CMV isolates recovered from these tissues were studied for genetic relatedness by Southern blot analysis of CMV DNA using ^{32}P-labeled probes made from plasmid-cloned CMV DNA fragments.

As shown in the table, tissue samples from each of the four patients had at least two different strains of CMV. These results indicate that exogenous reinfection with CMV does occur in AIDS patients. In a study reported by Plotkin et al., two renal transplant recipients were found to excrete different strains of CMV from different sites. These results suggest that exogenous reinfection may occur in these highly immunocompromised patients as well (Plotkin SA, Smiley ML, Friedman HM, et al: in Plotkin SA (ed): CMV, Pathogenesis and Prevention of Human Infection. Alan R. Liss, New York, 1984).

CMV ISOLATES FROM HOMOSEXUAL MEN WITH AIDS

Patient	Diagnosis	Tissue	Isolate Type*
1. LC	KS	KS tumor	A
		Lung	B
		Prostate	B
2. JT	KS	Lung	C
	PCP	Prostate	D
3. GR	KS	Lung	E
		Prostate	F
4. RG	KS	Prostate	G
		Kidney	H

Abbreviations: CMV, cytomegalovirus; KS, Kaposi's sarcoma; PCP, Pneumocystis carinii pneumonia.

* Different strains by restriction digest analysis.

To determine whether CMV contributes to the pathogenesis of AIDS, it will be important to determine if exogenous reinfection with CMV occurs in healthy homosexual men. We are currently pursuing this objective in a prospective study.

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ULTRASTRUCTURAL MARKERS IN AIDS

Considerable interest has been engendered by the intracytoplasmic inclusions --tubuloreticular structures (TRS), test tube and ring-shaped forms (TRF), vesicular rosettes (VR), and virus-like particles (VLP)--observed in tissue specimens taken from AIDS patients (Sidhu GS, Stahl RE, El-Sadr W, et al: Lancet, 1983, 1:990-991; Orenstein JM: Lancet, 1983, 2:284-285; Kostianovsky M, Kang YH, Grimley PM: Ultrastruct Pathol., 1983, 4:331-336; Ewing EP Jr, Spira TJ, Chandler FW, et al: N Engl J Med., 1983, 308:819-822; Feremans W, Menu R, Dustin P, et al: Lancet, 1983, 2:52-53; Gardiner T, Kirk J, Dermott HE: Lancet, 1983, 2:963-964). This report describes such inclusions in over 125 specimens from AIDS patients, homosexual men with lymphadenopathy and/or systemic symptoms and reversed T4:T8 ratios, asymptomatic homosexual men, hemophiliacs, and controls. The specimens were studied by transmission electron microscopy.

TRS were observed in all 27 specimens from 18 AIDS patients. These included specimens of lymph node, buffy coat, lung, thymus, and small cell carcinoma of the rectum. TRS were readily found in endothelial cells in all of the tissue

samples and in up to 30% of the lymphocytes in the lymph nodes and buffy coats. TRS were also observed in at least one specimen from 12 homosexual men, one bisexual man, and five proclaimed heterosexual men with lymphadenopathy and/or systemic symptoms but without AIDS, and in one healthy hemophiliac. Ten of these patients had reversed T4:T8 ratios of 1.2 or less.

TRF were observed in 17 specimens from 13 AIDS patients from whom either lymph node (5), buffy coat (2), thymus (1), or lung with bronchial mucosa (9) specimens were available for study. To our knowledge, this is the first report of TRF in the bronchial epithelium (Jackson D, Tabor E, Gerety FJ: Lancet, 1979, 1:1249-1250; Shimizu YK, Feinstone SM, Purcell RH, et al: Science, 1979, 205:197-200; Shamoto M, Murakami S, Zenke T: Cancer, 1981, 47:1804-1811; Prineas JW, Wright RG: Lab Invest., 1978, 38:409-421).

There appears to be an association between TRS and TRF in specimens from AIDS patients: TRF are not observed in the absence of TRS, the two types of inclusions are often in the same cell, and they are occasionally in close proximity. In many studies, TRS have been most readily found in endothelial cells. However, in this laboratory, TRF have never been observed in endothelial cells, even in samples rich in TRF-positive mononuclear cells. TRF were reported as rarely observed in endothelial cells in one published study, although this was not illustrated (Ewing EP Jr, Spira TJ, Chandler FW, et al: Lancet, 1983, 2: 285). There also has been no mention of TRF in the in vitro systems in which TRS have been induced readily by alpha-interferon (α-IFN) (Grimley PM, Yang Y-H, Silverman RH, et al: Lab Invest., 1983, 48:30A; Rich SA, Science, 1981, 213:772-775).

Although TRF were common in bronchial epithelia, we have observed only a single TRS in one bronchial cell. In transbronchial biopsies from two AIDS patients, the epithelial cells contained TRF as well as small numbers of structures identical to "attaching curved membranes" (type II) (Pfeifer U, Thomssen R, Legler K, et al: Virchows Arch., 1980, 33:233-243). These structures are considered by Pfeifer et al. to be the precursors of TRF in the chimpanzee non-A, non-B (NANB) hepatitis system. The two AIDS patients were not known to have NANB hepatitis. To our knowledge, this is the first description of these structures in clinical materials (Chandra S: Lab Invest., 1968, 18:422-428; Smith RD, Deinhardt F: J Cell Biol., 1969, 41:269-279).

VR were not observed in any specimens. VLP, which are morphologically identical to multivesicular bodies, were observed in a wide variety of cell types in every specimen. Their prevalence appeared to reflect the "activated" state of the cells, particularly lymphocytes and macrophages.

An additional "tubular" structure, apparently not previously described, was observed in a small percentage of mononuclear cells in five of five lymph nodes from AIDS patients and in the thymus of another. They were also seen in nine of 14 TRS-positive lymph nodes from seven of 12 non-AIDS TRS-positive patients, and in the lymph nodes of two of three asymptomatic homosexual men without AIDS or other disease markers. These aperiodic structures were either straight or undulating. They were approximately 20 nm thick and appeared to be free in the cytoplasm. On cross-section, clusters of these structures often had a regular arrangement. They were only occasionally seen in cells containing TRS and/or TRF. They were

never observed in buffy coat cells, even from patients with positive lymph nodes.

The significance of one or more of these structures to the etiology of AIDS is unknown. A key question regarding our findings is whether the appearance of TRS alone or together with TRF antedates the development of AIDS in individuals at risk and thus serves as an important surrogate marker for this disease. At this institution, one AIDS patient with Kaposi's sarcoma had a TRS/TRF-positive lymph node over 1 month before a diagnosis of AIDS was made. Ewing et al. (Ewing EP Jr, Spira TJ, Chandler FW, et al: Lancet, 1983, 2:285) reported similar findings in four patients. Currently, four patients with TRF-positive specimens (6 buffy coats in one, 2 buffy coats in another, and single lymph nodes in two) are being followed for the possible development of AIDS. A longitudinal study is needed for comparing the presence of the various ultrastructural markers with levels of suggested biochemical markers, such as α-IFN (DeStefano E, Friedman RM, Friedman-Kien AE, et al: J Infect Dis., 1982, 146:451-455; Buimovici-Klein E, Lange M, Klein RJ, et al: Lancet, 1983, 2:344) and thymosin α1 (Biggar RJ, Taylor PH, Goldstein AL, et al: N Engl J Med., 1983, 309:49-50; Hersh EM, Reuben JM, Rios A, et al: N Engl J Med., 1983, 308: 45-46) in large numbers of persons at risk for developing AIDS. Buffy coats, which are readily available through venipuncture, are the ideal specimens for use in studying these patients.

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THYMOSIN α1 BUT NOT β2-MICROGLOBULIN IS ELEVATED IN HOMOSEXUAL MEN WHO ARE AT RISK FOR AIDS

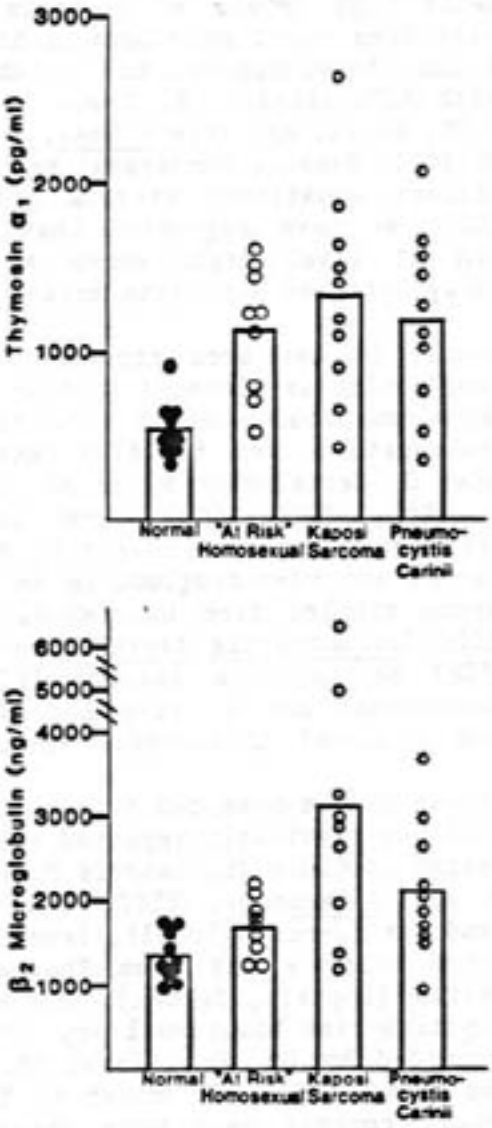
We have previously reported elevated levels of thymosin α1 in individuals with AIDS (Naylor PH, Goldstein AL: Clin Immunol Newsletter, 1983, 4(9):126-128). Abnormally high levels of thymosin α1 have also been found by others in homosexual men, hemophiliacs, and in children with AIDS (Kreiss JK, Lawrence DN, Kasper CK, et al: Ann Intern Med., 1984, 100:178-182). Because homosexual men and hemophiliacs constitute at-risk groups for AIDS, we have suggested that the thymosin α1 level might serve as an early diagnostic or surrogate marker for AIDS.

Recently it has been reported that β2-microglobulin is elevated in AIDS and that β2-microglobulin might also serve as a surrogate marker for AIDS (Bhalla RB, Safai B, Mertelsmann R, et al: Clin Chem., 1983, 29(8):1560). We have, therefore, evaluated the levels of both thymosin α1 and β2-microglobulin in the same serum samples from homosexual men with AIDS (Pneumocystis carinii pneumonia [PCP] or Kaposi's sarcoma [KS]), from homosexual men at risk for AIDS, and from a normal heterosexual control group.

Thymosin α1 was measured by a modification of our previously reported radioimmunoassay (McClure JE, Lameris N, Wara DW, et al: J Immunol., 1982, 128:368-375), and the β2-microglobulin level was determined using a kit from Pharmacia Diagnostics (Uppsala, Sweden). The sera from the high-risk homosexual population were provided by Dr. Evan Hersh (M. D. Anderson Cancer Center, Houston, TX). The normal control sera were obtained from the Red Cross Blood Center (Washington, DC). Sera from the AIDS patients

were provided by Dr. A. Friedman-Kien (New York University, New York, NY).

The results (Figure) confirm previous reports of elevations of thymosin α1 levels in high-risk homosexual men and in AIDS patients. Many individuals with frank AIDS (KS or PCP) also had elevated β2-microglobulin levels. However, β2-microglobulin levels were not elevated in the high-risk homosexual population.



Thymosin α1 and β2-Microglobulin Levels in Four Populations

Although the β2-microglobulin level was elevated in a significant number of patients with AIDS, the level was not elevated in at-risk homosexual men at a time when the thymosin α1 level was clearly elevated. While elevation of β2-microglobulin could precede the initial diagnosis of AIDS, it does not occur prior to the elevation of thymosin α1. Thus, thymosin α1 may be an earlier marker of blood suspect for AIDS than is β2-microglobulin.

It is not surprising that a significant number of patients with AIDS have elevated serum levels of β2-microglobulin. β2-Microglobulin is elevated in a number of clinically abnormal states. In addition, most hemophiliacs as well as individuals with hepatitis antigen have elevated levels of β2-microglobulin.

To date, the events which cause thymosin α1 levels to be elevated in homosexual men and hemophiliacs who are at risk for AIDS and in adult and pediatric AIDS patients have not been elucidated. We suggest that longitudinal studies in large populations of individuals at risk for AIDS are warranted to determine whether serum levels of surrogate markers such as thymosin α1 and β2-microglobulin will be of use in identifying individuals who might be asymptomatic carriers of AIDS.

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HIGH INCIDENCE OF LYMPHADENOPATHIC KAPOSI'S SARCOMA IN AUTOPSY SERIES

Data released by the Centers for Disease Control (CDC) (see page 23) indicate that only about one-third of AIDS patients suffer from Kaposi's sarcoma (KS). Our experience with biopsy and autopsy specimens suggests that KS is far more frequent than that, raising the possibility that KS may be the common denominator of AIDS from a pathologic standpoint.

Between April 16, 1980 and October 15, 1983, we performed complete autopsies on 55 patients who died of AIDS as defined by strict CDC criteria (Morb Mort Weekly Rep., 1982, 31:507-514). Fifty-three were selected for analysis of KS lesions. The types of KS were divided into two categories: (1) classical (CKS) or familiar and (2) "inflammatory" (IKS). IKS has been described in the literature under a variety of terms (Tedeschi CG: Arch Pathol., 1958, 66: 656-684; Lubin J: Arch Pathol., 1971, 92:338-341).

Gross and microscopic examinations showed one or both types of KS lesions in 87% of lymph nodes and in 73% of spleens examined. KS lesions were also found in lung (28%), skin (26%), alimentary tract (25%), and liver (15%). In all, lesions of KS were found in 94% of patients in this series. Except for the central nervous system and the myocardium, virtually every type of tissue was at risk. In 10% of the cases, KS was considered to be the proximate cause of death; the other 90% died of a variety of opportunistic infections.

All of the patients with KS had IKS; only a third had CKS. Every patient with CKS also had IKS either in association with CKS or independent of CKS. Morphologic intermediates of the two forms of KS were readily identifiable, but it was impossible to establish that sequential evolution had occurred. Review of serial biopsies available in several cases did not clarify this association, since CKS and IKS were found both early and late in the disease.

We believe that the IKS lesions are bona fide manifestations of KS. The frequency of IKS lesions is three-fold higher than the frequency of CKS lesions. Based on our biopsy analyses of specimens from AIDS patients, we do not believe that our results can be dismissed as artifacts of autopsy procedures.

IKS was a rare manifestation of KS before the epidemic of AIDS. In our opinion, it is the commonest manifestation of KS in AIDS. Others have described in different terms lesions in lymph node biopsies that we would probably call IKS (Harris NL: N Engl J Med., 1984, 310:462-463; Guarda LA, Butler JJ, Mansell P, et al: Am J Clin Pathol., 1983, 79(5):559-568; Brynes RK, Chan WC, Spira TJ, et al: JAMA, 1983, 250(10): 1313-1317; Ioachim HL, Lerner CW, Tapper ML: Am J Surg Pathol., 1983, 7(6):543-553). In these reports, the patients with marked vascular proliferation in lymph nodes had a poor prognosis.

The possibility has been raised that KS is not a neoplasm (Costa J, Rabson AS: Lancet, 1983, 1:58). Many apparently doubt that IKS is neoplastic in nature. However, our autopsy results suggest to us that both IKS and CKS in AIDS patients are highly malignant neoplasms. None of the patients survived longer than 3 years after diagnosis. Many who survived more than a year after diagnosis and those who experienced opportunistic infections but died of KS were cachectic.

We believe the true incidence of IKS in this series of patients may have been underestimated, because IKS is sometimes

impossible to distinguish from an inflammatory process. It is possible that lymphadenopathic KS is present in all cases of AIDS and that decreases in T cell numbers result from destruction of T cell domains in lymph nodes and spleens by the neoplasm.

If KS is ubiquitous in AIDS, earlier diagnoses of AIDS in the absence of opportunistic infections might be made by pathologists. Consideration could then be given to treating KS as the underlying disease in AIDS.

A detailed report of the autopsy findings has been submitted for publication.

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INTERFERON IN KAPOSI'S SARCOMA--HOW IMPORTANT ARE IMMUNOLOGICAL MEASUREMENTS?

Epidemic Kaposi's sarcoma (KS) is a frequent accompaniment of AIDS (Fauci AS: Ann Intern Med., 1984, 100:92-106; Longo DL: Ann Intern Med., 1984, 100: 96-98). Impaired immune function is felt to be an important component in the causation of this malignancy. Interferon (IFN) has been found to exert a therapeutic effect in such patients, although the long-term effects of IFN therapy are not yet known (Krown SE, Real FX, Cunningham-Rundles S, et al: N Engl J Med., 1983, 308:1071-1076).

Two KS patients were treated with recombinant alpha-2 IFN, and their clinical responses and various immunologic parameters were evaluated. Both patient A (a 32-year-old man) and patient B (a 25-year-old man) suffered from widespread progressive KS. In each case a diagnosis of KS was proven by multiple biopsies of skin lesions (stage II A). Both men were otherwise healthy, and neither had suffered from opportunistic infections. Both had been working regularly at the time IFN therapy was started.

Thirty million units of recombinant alpha-2 IFN (Schering Corp., Kenilworth, NJ) were injected subcutaneously three times a week. Within 4 weeks, patient A appeared to be in complete remission with complete disappearance of all skin lesions. Biopsy 10 weeks after institution of IFN therapy proved this to be the case. The therapy was stopped and patient A returned to work. Clinical relapse was suggested by the reappearance of subcutaneous nodules 16 weeks later. For patient B, skin lesions completely disappeared after 18 weeks of therapy, except for a discolored area on the forearm. Biopsy revealed residual KS cells. The dose of IFN was reduced to 15 million units per injection to reduce fatigue, and patient B was able to return to work. No new lesions and no opportunistic infections appeared in either patient at any time during therapy.

Both patients had occasional fevers and flu-like symptoms. Patient A had an OKT4:OKT8 ratio of 0.71 with 487 helper-inducer cells/mm^3 at the start of therapy. When therapy was stopped, the OKT4:OKT8 ratio was 0.04 with only 25 helper-inducer cells/mm^3. The lymphocyte proliferative capacity (measured as a response to phytohemagglutinin) was impaired at each testing. In contrast, all immunological studies of patient B have been normal both before and during his treatment.

These two patients with KS had very different levels of immune functioning, yet both responded to IFN. In fact, patient A, with the greatest abnormalities

in tests of immunity, responded faster to therapy than did patient B. The toxicity of the drug was not noticeably different in the two patients. Both patients have already outlived the mean time to death for patients with AIDS in our region (Louisiana Department of Health and Human Resources, January 1984). Such findings suggest a need for better, perhaps more representative, immunoregulatory studies to assess the effects of therapy and prognosis in immunodeficient patients.

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HEMOPHILIA AND AN UNUSUAL CANCER

Immunoregulatory abnormalities, including AIDS, have been noted in patients with hemophilia (Daly HM, Scott GL: Lancet, 1983, 2:1190; DeShazo RD, Andes WA, Nordberg J, et al: Ann Intern Med., 1983, 99:159-164). The causes of the abnormalities have not been determined but may be related to transfusion of blood products (Curran JW, Lawrence DN, Jaffe HW, et al: N Engl J Med., 1984, 310:69-75). The affected hemophiliacs are not generally exposed to other risk factors associated with AIDS (DeShazo RD, Andes WA, Nordberg J, et al: Ann Intern Med., 1983, 99:159-164). We report the development of an aggressive lung cancer in a patient with hemophilia 5 months after intensive exposure to cryoprecipitate (but not factor VIII concentrate) prepared from the blood of voluntary donors.

The patient was a 54-year-old white male physician transferred to the Tulane Medical Center in May 1983 following an episode of severe coronary insufficiency. Hemophilia A had been diagnosed in 1954 after excessive postoperative bleeding complicated a routine appendectomy. He received 6 units of whole blood and an unknown quantity of lyophilized plasma. Subsequently, the patient developed hepatitis. The patient did not recall receiving blood products at any other time.

The patient was married, had two children, and practiced medicine in a small, middle-class community. He had no history of homosexuality, drug abuse, recent foreign travel, or contact with patients with AIDS. He had smoked a few cigarettes per day for less than 3 years and had not worked with silica or asbestos.

Physical examination was unremarkable and laboratory studies indicated a normal blood count and chest x-ray. The template bleeding time was 8 min (normal = 2-10 min), the factor VIII coagulant activity (FVIII:C) was 12% of normal, and the factor VIII related antigen level was 132% of normal.

After coronary arteriography revealed multiple high-grade stenoses of both right and left coronary arteries, the patient underwent quadruple aorto-coronary artery bypass grafting without complication. The patient was prepared for surgery with cryoprecipitate to achieve 100% FVIII:C levels. Postoperatively, cryoprecipitate was continued twice daily to keep the FVIII:C between 50% and 100%. The postoperative course was uneventful, and cryoprecipitate was discontinued on the seventh postoperative day. The patient returned home 4 days later. During the hospitalization, the patient received a total of 250 bags of cryoprecipitate, 10 units of random-donor platelets, 4 units of fresh-frozen plasma, and 7 units of

packed red blood cells. All blood was from voluntary donor sources.

The patient did well until September 1983 when he noted a small mass in the right side of his neck. One week later he developed hoarseness due to a paralyzed right vocal cord and was readmitted to the hospital. Physical examination revealed an ill-appearing man with fever, tachypnea, and an indurated mass in the right side of his neck. Chest x-ray revealed interstitial infiltrates in the lower fields of both lungs.

Adequate factor VIII levels were attained without difficulty using cryoprecipitate. The patient developed progressive hypoxemia with rapidly worsening interstitial infiltrates in both lung fields and an expanding right paratracheal mass. Thoracotomy with biopsy of a 5 × 4 cm mass in the right side of the neck and biopsy of a large mediastinal mass revealed metastatic, poorly differentiated adenocarcinomas, with frequent mitoses and blood vessel invasion. The same type of tumor was present in the lung with lymphangitic spread. No evidence of Pneumocystis carinii infection or cytomegalovirus infection was found. There was rapid worsening of respiratory distress and rapid enlargement of the tumor mass. Death from intractable respiratory failure occurred within 5 days of lung biopsy and within 5 months of the cardiac surgery.

Tests for the presence of various hepatitis antibodies and antigens were performed. Tests for HBcAB, HBsAB, and HBVAB were positive; tests for HBeAG, HBeAB, and HAVAB-IgM were negative. Three days before the patient's death and 3 days after the lung biopsy, an unusual pattern of lymphopenia was found in immunologic studies (Table). Peak lymphocyte mitogen responses to phytohemagglutinin were suppressed to 66% of normal when compared with the responses of simultaneously tested controls.

This patient had a rapidly fatal carcinoma of the lung. He had very few risk factors for such a malignancy. The unusual course of his disease and the

MONONUCLEAR CELLS IN A HEMOPHILIAC WITH AN UNUSUAL CANCER

Cell Subset	Monoclonal Specificity	Absolute No. Cells/mm^3	Patient	Control
			(%)	(%)*
T_{11}	Pan T (E rosette receptors)	360	16	60 ± 18
T_4	T helper-inducer	202	9	25 ± 8
T_8	T suppressor-cytotoxic	0	0	22 ± 9
Ia^+	Monocytes, activated T	405	18	27 ± 7
T_7	Natural killer	23	1	9 ± 6
B	B	36	16	11 ± 6

*Mean ± SD.

types of immunological impairments which developed suggest that he may have had an illness related to AIDS. Although reduced ratios of helper:suppressor T lymphocytes have been seen in patients who have undergone open heart surgery (Brody JI, Pickering NJ, Behr D, et al: Blood, 1983, 62:A109), this appears to be a transient phenomenon which returns to normal within 24 hr. Our patient's coronary bypass surgery had occurred 5 months earlier. Our patient was exposed to large amounts of cryoprecipitate and other blood products but was not exposed to commercial coagulation factor concentrate at the time of surgery.

No increases in malignancies in patients with hemophilia have been reported in the literature. However, there have been recent descriptions of immune changes in such patients (Ballard JO, Kelly GA, Kukrika MD, et al: Cancer, 1981, 48:686-690; Gordon EM, Berkowitz RJ, Strandjord SE, et al: J Pediatr., 1983, 103:75-76; Bart RS, Kopf AW: J Dermatol Surg Oncol., 1980, 6:894-895). Cases of hemophilia and hepatoma, Burkitt's lymphoma, and basal cell carcinoma have been reported, but descriptions of the transfusion histories and immune functions of the patients have not always been available. All patients with hemophilia who have developed AIDS have used coagulation factor concentrates; opportunistic infections have been widespread in these patients and are indicative of immune dysfunctioning. The follow-up of patients with hemophilia whose immune dysfunctions have been documented has been short and has not allowed for a determination of the frequency with which such abnormalities are associated with the development of (B cell?) lymphomas, carcinomas, or Kaposi's sarcomas (such as those seen in homosexual patients) (Fauci AS: Ann Intern Med., 1984, 100:92-106; Longo DL: Ann Intern Med., 1984, 100:96-98; Gascon P, Zoumbos NC, Young NS: Ann Intern Med., 1984, 100:173-177; Irwin LE, Begandy MK, Moore TM: Ann Intern Med., 1984, 100:158).

Close scrutiny of patients receiving blood transfusions (Gascon P, Zoumbos NC, Young NS: Ann Intern Med., 1984, 100:173-177) may provide a better understanding of the disease seen in our patient. Evaluation of the effects of therapy for hemophilia should perhaps be extended to the use of cryoprecipitate as well as commercial coagulation factor concentrates. Careful analysis of the status of patients receiving various blood products may be of use in determining the safest therapy for hemophilia and for other patients requiring blood transfusions.

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INFECTIOUS COMPLICATIONS IN AIDS: EXPERIENCE AT THE NEW YORK HOSPITAL-CORNELL MEDICAL CENTER

We reviewed the records of all patients admitted to The New York Hospital-Cornell Medical Center in whom the diagnosis of AIDS had been made. The CDC criteria were used for diagnosis (Morb Mort Weekly Rep., 1982, 31:507-514).

Stool specimens were taken from patients with diarrhea. Bacterial, viral, and fungal cultures were grown by the hospital diagnostic microbiology laboratory. Specimens were examined for ova and parasites and for cryptosporidia. Cryptosporidia were identified in the stools using a three-step procedure.

This includes the Sheather's sugar coverslip flotation technique for concentration, an iodine stain, and a modified Kinyoun acid-fast stain (Bates DV, Macklen PT, Christie RV: in Respiratory Function in Disease, 2nd ed, WB Saunders Co., Philadelphia, 1971).

Patients with pulmonary disease were studied in several ways: chest radiography, arterial blood gas analyses, sputum analyses (when sputum samples were available), pulmonary function tests, and, if indicated, bronchoscopy and/or open lung biopsy (Stover DE: Ann Intern Med., 1984, in press). Bronchial washings were obtained randomly in the airways by instilling and suctioning back 5-10 cc of normal saline. Bronchoalveolar lavage was accomplished by wedging the fiber optic bronchoscope into an involved segment of the lung and instilling a total of 210-280 cc of normal saline in 30 aliquots. Each aliquot was [illegible]trated back by general manual suction. The amount of lavage fluid used depended on the clinical situation. Transbronchial brushings and biopsies were performed under single plane fluoroscopic control. Brushings, washings, and lavage fluid were processed with bacterial, fungal, and viral stains and were also cultured for these organisms. In addition, lavage specimens were tested for Legionella antigen and antibody using direct immunofluorescence techniques.

Ninety patients with AIDS were admitted to The New York Hospital by December 1983 (Table 1). Since no patient had been seen only in the out-patient department, this number represents the total number of patients observed in this center. Eighty patients were diagnosed as having AIDS with opportunistic infections (OI) (alone, with Kaposi's sarcoma [KS], or with lymphoma); three other patients had KS alone, and seven had lymphoma alone.

TABLE 1
PATIENT POPULATION WITH AIDS

Diagnosis at Presentation	No. of Patients
OI	52
OI and KS	20
OI and lymphoma	8
Total OI	80
KS alone	3
Lymphoma	7
Total patients	90

Abbreviations: OI, opportunistic infection; KS, Kaposi's sarcoma.

Figure 1 shows the admission dates for all patients seen since 1979. In the first 6 months of 1979, a single pa-

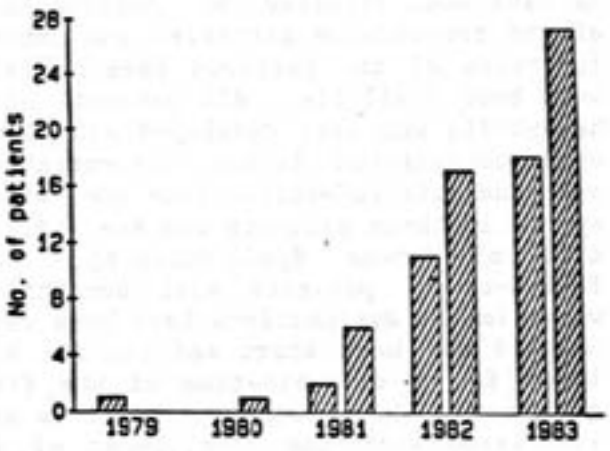

Fig. 1. AIDS--Opportunistic Infections by Admission Date

tient with AIDS was admitted. None were seen in the last 6 months of 1979 and the first 6 months of 1980. A second patient was seen in the fall of 1980. In the spring of 1981, two patients were observed, and six were seen in the fall of that year. The number of patients seen has progressively increased; in the last 6-month period, 27 new patients have been admitted.

The frequencies of the various opportunistic infections in our study population of 80 patients are given in Table 2.

TABLE 2
FREQUENCY OF
OPPORTUNISTIC INFECTIONS

Infection	No. of Infections
Pneumocystis carinii pneumonia	59
Candidiasis	
Thrush and/or esophagitis	57
Disseminated	5
Disseminated CMV (12/32 at post mortem)	32
Herpes simplex virus (perirectal)	14
Mycobacterium avium intracellulare	18
Cryptococcosis	6
Cryptosporidiosis	8
Toxoplasmosis	4
Salmonella bacteremia	4
Aspergillosis (4/4 at post mortem)	4

Abbreviation: CMV, cytomegalovirus.

The most common infections were Pneumocystis carinii pneumonia, candidiasis, and disseminated CMV.

Most patients had several infections. The number of patients showing from one to six infections is given in Table 3.

TABLE 3
MULTIPLICITY OF
OPPORTUNISTIC INFECTIONS

No. of OI	No. of Patients with Indicated No. of OI
1	16
2	29
3	12
4	14
5	6
6	2

Abbreviation: OI, opportunistic infection.

Fifty-seven and one-half percent (46/80) of the total patient population had died by December 31, 1983. Figure 2 shows the time of death after the onset of OI for the 46 patients who died. A more accurate estimate of the true mortality is given by the statistic that 97.2% (35/36 patients) with disease onsets before December 31, 1982 had died by December 31, 1983.

OI are the most frequent of the clinical manifestations of AIDS. Their presence also constitutes one of the methods of diagnosis of the disease. Scattered reports dealing with specific clinical aspects of AIDS have appeared previously. The perspective gained by evaluation of a large series of patients studied in a single institution has been reported in this paper.

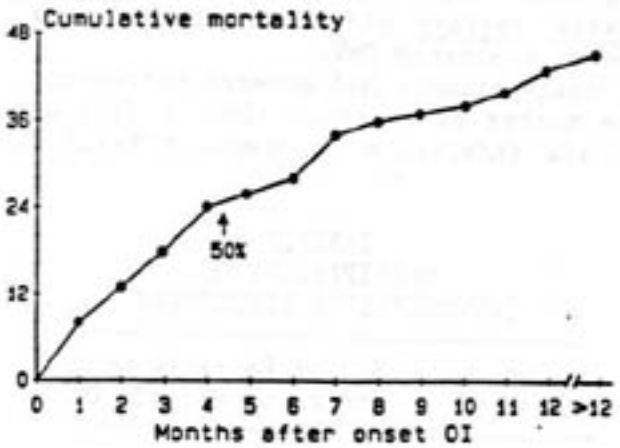

Fig. 2. Mortality After Onset of Opportunistic Infections, 1978-1983

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UPCOMING AIDS MEETING

Symposium: Critical Gay and Lesbian Health Problems
August 22-25, 1984
Marriott Hotel
Chicago, Illinois

Scientific Program Co-Sponsored by American Association of Physicians for Human Rights and National Coalition of Gay Sexually Transmitted Diseases Services in association with the annual meeting of the AAPHR

Information/Registration:
Mr. Doug Carner
AAPHR, P.O. Box 14366 .
San Francisco, CA 94114
(415) 558-9353

Topics: Etiology, Diagnosis, Immunology, Therapeutic Trials and Alternative Treatments, Psychological Aspects, and Sociology of AIDS; Lymphadenopathy Syndrome and Its Relationship to AIDS; The Hepatitis B Vaccine and AIDS; Hepatitis B Infection in Gay Men; Overview of NIH's AIDS Research Programs; Gay Community Medical Organizations in AIDS Research and Prevention; Intestinal Syndromes in Gay Men; Lesbian Health Issues; Helping Gay and Lesbian Youth Attain Positive Self Images; Stages of Gay and Lesbian Relationships; Impaired Gay and Lesbian Physicians; Gay Parenting; Social and Political Barriers to Gay and Lesbian Healthcare.

Speakers: Drs. R. Krause, R. Enlow, W. Blumenthal, P. Volberding, K. Mayer, W. Siroty, S. Follansbee, M. Forstein, D. Abrams, E. Harrison, M. Kirkpatrick, K. Sell, C. Stevens, T. Quinn, R. Bolan, S. Nichols, J. Sonnabend, P. Robertson, D. Ostrow, D. McWhirter, D. Mattison, N. Schram, D. Martin, M. Ross, M. Pohl, E. Hetrick, D. Stewart, P. Paroski, and M. Schneider.

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF April 23, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1043	25.0	255	24.4
PCP without KS	2166	51.9	1017	47.0
Both KS and PCP	278	6.7	175	63.0
OI without KS or PCP	690	16.5	360	52.2
TOTAL	4177	100.0	1807	43.3

KS = Kaposi's sarcoma
OI = Opportunistic infection
PCP = Pneumocystis carinii pneumonia

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	2999	76.9	0	0.0	2999	71.8
IV drug user	580	14.9	154	55.8	734	17.6
Haitian	143	3.7	24	8.7	167	4.0
Hemophiliac	30	0.8	0	0.0	30	0.7
No apparent risk group or unknown	149	3.8	98	35.5	247	5.9
TOTAL	3901	100.0	276	100.0	4177	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

INSTRUCTIONS FOR AUTHORS CONTRIBUTING TO THE AIDS MEMORANDUM

Content: Articles published in the AIDS Memorandum must have obvious relevance to AIDS. They can describe clinical or experimental findings. Letters and other types of commentary are also welcome. All manuscripts should be typed double spaced.

References: References should be integrated into the text in parentheses. Each citation should include the names of up to three authors, the journal title, the year of publication, volume and issue numbers, and inclusive page numbers. Citations from books should include the names of up to three authors, book title, editor(s), publisher, publisher's location, year of publication, and relevant page numbers.

Tables and Figures: Whenever possible, data should be organized into tables. Figures should be clear and no wider than 3¼ inches.

Announcements of Meetings: Announcements of upcoming AIDS meetings should include meeting title, location, and date and the name, address, and telephone number of the organizer of the meeting.

Further Information: For further information call the AIDS Memorandum office at (301) 496-9537.

Mailing Instructions: Manuscripts for the AIDS Memorandum should be sent to this address:

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